ALLIA.143

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#12 Decl.

Applicant	:	H. Zaghouani	)	Group Art Unit 1806
Appl. No.	:	08/779,767	)	
Filed	:	January 7, 1997	)	
For	:	COMPOUNDS, COMPOSITIONS, AND METHODS FOR THE ENDOCYTIC PRESENTATION OF IMMUNOSUPPRESSIVE FACTORS	)	
Examiner	:	J. Reeves	)	

Declaration Under 35 U.S.C. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I Catherine M. Woods, Ph.D. declare and state:

1. This declaration is submitted to establish the specification of the above identified application enables one skilled in the art to make and use compositions comprising an immunoglobulin or a portion thereof linked to a protein fragment or peptide, wherein the immunoglobulin or portion thereof is capable of binding to the Fc receptor and the protein fragment or peptide comprises a T cell receptor antagonist, and wherein the composition has the property of being endocytosed by cells bearing an Fc receptor and processed by said cells to present at least a portion of said protein fragment or peptide in association with endogenous MHC Class II molecules.

2. I am the Director of Cellular and Molecular Biology at Alliance Pharmaceutical Corp., San Diego, CA, a licensee of the present application. A copy of my curriculum vitae is attached as Exhibit A. I have extensive research experience in the fields of molecular biology and hematology as evidenced by Exhibit A.

3. I am familiar with the specification and claims of the above-identified application and its prosecution history.

4. The terminology "analog" as applied to analogs of peptide agonists capable of activating a T cell response has a well defined meaning to the skilled artisan. That is, those skilled in the art recognize that such an "analog" is a peptide which shares significant structural and functional homology with the agonist, such as an antigen associated with autoimmune disease, but which varies with respect to certain features of the other peptide. For example, an analog of a peptide agonist capable of activating a T cell response may have sufficient structural and functional homology to the agonist to permit it to be bound by T cells expressing T cell receptors which bind to the agonist while lacking the ability to activate such T cells. Those skilled in the art recognize that the term "analog" does not include a single amino acid or a single amino acid side chain.

5. Thymic selection refers to a process through which immature T cells in the thymus which recognize self-antigens are deleted from the population. The compositions of the present invention act downstream of thymic selection at the level of mature peripheral T cells. Accordingly, the compositions of the present invention operate outside of the sphere of thymic selection and references which relate to thymic selection are immaterial to the mechanisms through which the present compositions exert their effects.

6. Those skilled in the art are capable of determining which self antigens are associated with particular autoimmune diseases, constructing peptide analogs of such self-antigens, screening such peptide analogs in vitro and in vivo to identify those which act as T cell receptor antagonists, and incorporating the identified T cell receptor antagonists in the compositions of the present invention. Each of these steps may be routinely accomplished by following the procedures set forth in the specification of the above-identified application and by using techniques which were known to those skilled in the art at the time the above-identified application was filed.

Methods for identifying peptide antigens associated with autoimmune disease were known to those skilled in the art at the time the above-identified application was filed. The articles by Richert, Tuohy, Liblau, Hudrisier et al., and Gautam et al. provided in Exhibit B are representative of a number of articles describing the identification of peptides associated with human autoimmune diseases and the characterization of peptides capable of binding the T cell receptor. In addition, as of the filing date of the above-identified application, those skilled in the art were capable of generating a large library of peptides to be screen for activity as T cell receptor antagonists using combinatorial chemistry.

Following the identification of peptide antigens associated with autoimmune diseases using the methods described in the articles cited above, analogs of these peptides which function as T cell receptor antagonists may be identified using techniques known to those skilled in the art at the time the above-identified application was filed. The articles by Sette et al., Liu and Wraith, and Karin et al., provide representative examples of the construction and characterization of peptide analogs which act as T cell receptor antagonists. Further examples of the construction and characterization of T cell receptor antagonists are provided by the abstracts of Windhagen et al., Tsitoura et al., Madrenas et al., and the two abstracts by Sloan-Lancaster et al., each of which are also provided in Exhibit B.

Methods for screening T cells from individuals suffering from autoimmune disease to identify the self-antigens against which they are directed are described in Czerkinsky et al, Olsson

et al., Link et al., and Soderstrom et al. which are included in Exhibit B. Such methods may also be used to evaluate the response of the T cells directed against self-antigens to peptide analogs in order to identify analogs which act as T cell receptor antagonists.

The specification describes the preparation of peptides and peptide analogs to be used in the compositions of the present invention (Example I), the production of chimeric immunoglobulins comprising the peptides and peptide analogs (Example II), the confirmation that the resulting chimeric antibodies include the peptides or peptide analogs (Examples III-V), *in vitro* assays for evaluating the ability of the chimeric immunoglobulins to present the peptides or peptide analogs to T cells (Examples VI and VII), *in vitro* assays for evaluating T cell inhibition by chimeric immunoglobulins containing T cell receptor antagonists (Example VIII), and *in vivo* methods for evaluating the ability of a chimeric immunoglobulin to inhibit the T cell response to an antigen associated with autoimmune disease.

Accordingly, using the techniques disclosed in the specification in combination with methodologies in existence at the time the above-identified application was filed, those skilled in the art are enabled to make and identify T cell receptor antagonists and to make and use the compositions claimed in the above-identified application.

7. Experimental allergic encephalomyelitis in the SJL mouse is a standard animal model used by those skilled in the art for evaluating potential therapeutic agents for the treatment of an autoimmune disorder, multiple sclerosis. Example XI of the above-identified specification provides statistically significant results indicating the claimed compositions are effective in inhibiting T cell activation in the SJL mouse.

8. Tolerization is a phenomenon in which non-professional antigen presenting cells lacking the Fc receptor which may not be capable of processing antigens induce tolerance of a self-antigen. In contrast, the present compositions act via professional antigen presenting cells such as dendritic cells and B cells, which express the Fc receptor and which are capable of processing antigens and presenting them in the context of the MHC Class II proteins. Accordingly, references speculating that antibodies having a self-antigen inserted into their CDRs may be able to tolerize do not disclose or suggest the claimed compositions.

9. I understand that this declaration is being submitted before final rejection of the above-identified application.

10. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: May 29, 98

By: Catherine M. Woods, Ph.D.